REMARKS

Support for Amendment to the Specification

Support for the amendment to the paragraph bridging pages 10 and 11 may be found in the second full paragraph on page 10.

Support for Claim Amendments

Support for the amendment of Claim 1 may be found in Claim 1 as filed.

Response to Restriction Requirement

Applicant confirms the provisional election with traverse, by Pat DeSimone on 2/14/03, of Group I, Claims 1-37.

Species Election Requirement

Applicant confirms the provisional election with traverse, by Pat DeSimone on 2/14/03, of the species of the composition being oridonin from Rabdosia rubescens and the extract of Humulus lupulus. Applicant believes that Claims 1-37 are readable on these species elections.

Claim Rejections Under 35 U.S.C. § 102(b)

Claims 1-3, 5-8, 11-16, 18-23, 26-29, and 32-35 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by GB 1476016. Applicants respectfully traverse this rejection.

GB 1476016 to Fujita et al. ("Fujita") discloses the use of oridonin and lasiokaurin as antitumor agents.

To anticipate a claim, a reference must disclose each and every element of the claim. *Lewmar Marine v. Varient Inc.*, 3 USPQ2d 1766 (Fed. Cir. 1987). Fujita does not anticipate Claim 1 because it does not teach each and every element of Claim 1. Claim 1 has been amended to recite the presence of oridonin, a pharmaceutically acceptable salt or ester of oridonin, a selectively substituted analog of oridonin, or a combination

thereof; and lupulone, a pharmaceutically acceptable salt or ester of lupulone, a selectively substituted analog of lupulone, or a combination thereof. Fujita does not teach lupulone, a pharmaceutically acceptable salt or ester of lupulone, or a selectively substituted analog of lupulone. Therefore, Fujita cannot anticipate Claim 1. Given that Claims 2, 3, 5-8, 11-16, 18-23, 26-29, and 32-35 each depend ultimately from and further limit Claim 1, Applicants respectfully request the reconsideration and withdrawal of the rejection of Claims 1-3, 5-8, 11-16, 18-23, 26-29, and 32-35 under 35 U.S.C. §102(b) over Fujita.

Claims 1, 5-9, 11-16, 18-24, 26-30, and 32-36 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by JP 57-167938. Applicants respectfully traverse this rejection.

According to the abstract provided with the office action, JP 57-167938 discloses that oridonin exhibits carcinostatic activity. JP 57-167938 does not teach lupulone, a pharmaceutically acceptable salt or ester of lupulone, or a selectively substituted analog of lupulone. Therefore JP 57-167938 cannot anticipate Claim 1. Given that Claims 5-9, 11-16, 18-24, 26-30, and 32-36 each depend ultimately from and further limit Claim 1, Applicant respectfully requests the reconsideration and withdrawal of the rejection of Claims 1, 5-9, 11-16, 18-24, 26-30, and 32-36 under 35 U.S.C. §102(b) over JP 57-167938.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1-37 stand rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over JP 57-167938, GB 1476016, or JP 352102434 taken with JP 11-236334 or JP 52-145509. Applicants respectfully traverse this rejection.

GB 1476016 (Fujita) and JP 57-167938 are discussed above. JP 52-102434 [cited as JP352102434] is based on the same Japanese Patent Application to which priority is claimed in GB 1476016 to Fujita (i.e., the two references belong to the same patent family). Thus, like Fujita, JP 52-102434 apparently discloses the use of oridonin as an antitumor agent. According to the abstract provided with the office action, JP 11-236334

discloses the use of twenty-three plants or their extracts as cell adhesion inhibitors or cancer metastasis inhibitors; the plants include, inter alia, Humulus lupulus. According to the abstract provided with the office action, JP 52-145509 alleges that "a bitter principle of hops of Humulus lupulus" exhibits an anti-cancer effect for cancers of the stomach, liver, lunch and breast.

Applicants respectfully assert that a prima facie case has not been established because there is no motivation to combine the cited references, because the reference combination represents an impermissible obvious-to-try suggestion, and because the cited references do not collectively provide an expectation of success for Applicant's invention.

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing a prima facie case of obviousness. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Establishing a prima facie case of obviousness requires that all elements of the invention be disclosed in the prior art. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A 1970). Applicant's Claim 1 recites the presence in the composition of "lupulone, a pharmaceutically acceptable salt or ester of lupulone, a selectively substituted analog of lupulone, or a combination thereof." None of the cited references teach or suggest this limitation. Thus, the cited references collectively fail to teach all elements of Claim 1.

There is no motivation to combine the cited references. Establishing a prima facie case based on multiple references requires the Patent Office to show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art [that] would lead that individual to combine the relevant teachings of the references." *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Such an objective teaching is absent here. To the contrary, the conflicting teachings of the references would teach away from their combination. Note in particular that JP 57-167938, GB 1476016, and JP 52-102434 teach pharmaceutical compositions containing the compound oridonin as a pharmaceutically active ingredient, whereas JP 11-236334 or JP 52-145509 teach the use of plants or their extracts, apparently as dietary supplements, without specifying any active compounds. One of ordinary skill in the art formulating a pharmaceutical

compound would not add a raw plant material or a crude plant extract. Likewise, one of ordinary skill in the art formulating a plant-based dietary supplement would not add a purified chemical compound. Thus, the different forms of the compositions and their different uses teach away from the suggested combination of references. The only conceivable motivation for combining the references is hindsight, but the Federal Circuit has consistently held that it is impermissible to "use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *Ecolochem Inc. v. Southern California Edison*, 56 USPQ2d 1065, 1072 (Fed. Cir. 2000)(quoting *In re Fine*, 5 USPQ2d 1780, 1783 (Fed. Cir. 1988)). The suggestion to combine the pharmaceutical compositions of JP 57-167938, GB 1476016, and JP 52-102434 with the plant-based compositions of JP 11-236334 or JP 52-145509 thus represents an impermissible "obvious to try" suggestion that does not satisfy the requirements of a prima facie case. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). As there is no motivation to combine the cited references, a prima facie case has not been established.

Furthermore, a prima facie case has not been established because the cited references provide no expectation of success for Applicant's invention. "Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *In re Dow Chemical*, 5 U.S.P.Q.2d 1529, 1531 (C.A.F.C. 1988). The cited references provide no expectation of success for the combination of oridonin (or salt, ester, or analog thereof) and lupulone (or salt, ester, or analog thereof) recited in Applicant's Claim 1. Furthermore, the pharmaceutical arts are notoriously unpredictable. *Application of Riat*, 327 F.2d 685, 686 (C.C.P.A. 1964); *Application of Kamal*, 398 F.2d 867, 871 (C.C.P.A. 1968). For example, agents that are effective individually may be antagonistic when used in combination. *See e.g.* D. R. Budman, A. Calabro, and W. Kreis, "Synergistic and antagonistic combinations of drugs in human prostate cancer cell lines in vitro," Anticancer Drugs, volume 13, number 10, pages 1011-1016 (2002); M. Distefano, C. Ferlini, R. De Vincenzo, C. Gaggini, S. Mancuso, and G. Scambia, "Antagonistic effect of the combination of gemcitabine/topotecan in ovarian cancer cells," Oncology Research, volume 12, number 9-10, pages 355-359 (2000). The cases cited by the Examiner regarding the combination of multiple ingredients are therefore

distinguished as not pertaining to the notoriously unpredictable pharmaceutical arts. *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (C.C.P.A. 1972)(relating to a combination of surfactants); *In re Susi*, 58 CCPA 1074, 1079-80, 169 USPQ 423, 426 (C.C.P.A. 1971)(relating to light stable polymers); *In re Crockett*, 279 F.2d 274, 276-277, 126 USPQ 186, 188 (C.C.P.A. 1960)(relating to use of magnesium oxide and calcium carbide in cast iron). In summary, the cited references, taken together with the knowledge of one skilled in the art of cancer treatment and considered in light of the unpredictability of the pharmaceutical arts, provide no expectation of success for Applicant's Claim 1 composition.

For all of the foregoing reasons, a prima facie case has not been established, and Claim 1 is therefore patentable over the cited references. Given that Claims 2-37 each depend ultimately from and further limit Claim 1, they, too, are patentable over the cited references. Applicant therefore respectfully requests the reconsideration and withdrawal of the rejection of Claims 1-37 under 35 U.S.C. § 103(a), as allegedly unpatentable over JP 57-167938, GB 1476016, or JP 352102434 taken with JP 11-236334 or JP 52-145509.

New Claims

Claim 48 has been added to further claim the invention. Support for the Claim may be found in Claim 1 as filed.

It is believed that the foregoing amendments and remarks fully comply with the Office Action and that the claims herein should now be allowable to Applicants. Accordingly, reconsideration and allowance is requested.

If there are any additional charges with respect to this Amendment or otherwise, please charge them to Deposit Account No. 06-1130 maintained by Applicants' attorneys.

Respectfully submitted,

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